

Diagnostic value of transcranial sonography for patients with Parkinson's disease in the chinese population: A meta and meta-regression analysis

Bo Liu, Wenjing Luo, Yingmin Mo, Chunying Wei and Min Han*

The Cadre ward in Department of Neurology, the people's hospital of guangxi zhuang autonomous region, No.6, Tao Yuan Road, Nanning, Guangxi, 530021, China

Abstract

Background: To evaluate the diagnostic accuracy of substantia nigra hyper-echogenicity by transcranial sonography (TCS) for the diagnosis of Parkinson's disease (PD) in the Chinese population.

Methods: We searched the electronic databases of Cochrane Central Register of Controlled Trials (CENTRAL), Pubmed, Embase, China National Knowledge Infrastructure (CNKI), Chinese Biomedical Database (CBM) up to Dec 2018 for related articles. All the published population-based studies investigating diagnostic value of TCS for PD patients in China were searched and evaluated. A meta and meta-regression analysis was performed to calculate the available data from each research. Meta—Disc 1.4 statistics software was used.

Results: 23 studies with 1478 PD patients were analyzed. The pooled sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR-) and diagnostic odds ratio (DOR) of TCS were 0.78 (95% confidence interval (CI): 0.75, 0.80), 0.87 (95% CI: 0.85, 0.89), 6.74 (95% CI: 5.04, 8.31), 0.23 (95% CI: 0.19, 0.28) and 31.32 (95% CI: 21.28, 46.09), respectively, for differentiating PD patients from healthy controls. The AUC and Q-index was 0.9119 and 0.8442, respectively. In the subgroup and meta-regression analysis, we found that the important cause of heterogeneity was the sample size of PD patients (P=0.0051).

Conclusion: TCS is an effective and useful tool to detect and distinguish PD from healthy controls in the Chinese individuals.

Introduction

Parkinson's disease (PD) is the second most prevalent neurodegenerative disease in the world and is associated with the progressive loss of dopaminergic neurons in the substantia nigra (SN) [1]. Diagnosis of PD is usually based on clinical criteria [2]. A recent clinical pathology study demonstrated that in the early stage of the disease, only 50% PD patients received an accurate diagnosis of PD [3]. Besides, in specialized movement disorder centers, PD is wrongly diagnosed in 6 to 25% of cases [4]. The most diagnostic confusing diseases are atypical parkinsonian disorders (APD), including progressive supranuclear palsy (PSP), multiple system atrophy (MSA), corticobasal ganglionic degeneration (CBD) and dementia with Lewy bodies (DLB) [5-7]. Therefore, to improve the accuracy of the clinical diagnosis, there is a need to have a reliable and practical reference standard. Recently, several different diagnostic tools have been evaluated in their ability to detect nigrostriatal cell loss. TCS is one of the most widely used tests, which is a convenient and noninvasive diagnostic technique that allows imaging of the brain parenchyma in twodimensional black and white slices [8]. Moreover, some articles had reported substantia nigra hyperechogenicity in PD and assessed the diagnostic accuracy of TCS [9,10]. But, most of evidences came from European and American. Until now, there were only a few evidences on Chinese individuals, and the conclusions were discrepant [11,12]. Consequently, we conducted a meta-analysis to estimate the clinical utility of TCS in the Chinese PD individuals.

Materials and methods

Literature search

Eligible studies were identified by searching in the Cochrane Central Register of Controlled Trials (CENTRAL), Pubmed, Embase, China National Knowledge Infrastructure (CNKI), Chinese Biomedical Database (CBM) for relevant trials without language restrictions using the following mesh search terms: "transcranial sonography" or "TCS", "Parkinson's disease" or "PD". Terms were exploded whenever possible in each database. We fixed Dec. 2018 as the cut-off date for inclusion of studies.

Inclusion criteria for relevant studies

Studies were included if they met all of the following criteria: (1) Studies needed to assessed the ability of the TCS. (2) Diagnostic differentiation between PD and controls, the diagnosis of PD was made according to the United Kingdom Parkinson's Disease Society Brain

***Correspondence to:** Min Han, the Cadre ward in Department of Neurology, the people's hospital of guangxi zhuang autonomous region, No.6, Tao Yuan Road, Nanning, Guangxi, 530021, China, E-mail: bliu881215@163.com

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Bank Criteria [13] or the Movement Disorder and Parkinson's Disease Group of the Chinese Medical Association Branch of Neurology [14], (3) Original articles provided the extractable data on the diagnostic value of TCS in PD patients. (4) Clinical data regarding the publication year, ages, gender, sample size and diagnosis criteria was collected. (5) Studies would be excluded if the above information could not be obtained.

Outcome measures for this review

Two independent reviewers obtained full manuscripts of all citations that were likely to meet the predefined selection criteria. They independently reviewed the articles and extracted the data from the included studies. Areas of disagreement or uncertainty were resolved by discussion and consultation with a third reviewer. When multiple articles were published from a single study, we selected the report that contained the most complete and relevant data on the diagnostic value of TCS in PD patients. Two reviewers independently extracted the following data elements from each selected article: the study characteristics, number of PD patients and controls, and data regarding diagnostic value of TCS. The pooled sensitivity, specificity, LR+, LR- and DOR with 95% CI were calculated to estimate the diagnostic value of TCS in PD patients. We calculated statistical heterogeneity by an X² test on N-1 degrees of freedom with P<0.1 indicating significant heterogeneity [15]. To evaluate the heterogeneity, we also used the I² test, taking values in the range 0-100% [16]. I² values of 25% may be represent low, 50% modest, and 75% large heterogeneity, respectively [17]. When P ≥ 0.1 or I² ≤50% indicated a lack of heterogeneity, the fixed effect model was employed. Otherwise, the random effect model was chosen. Potential publication bias was examined using funnel plots [18]. A sensitivity analysis was also performed by repeating the meta-analysis and omitting each study at each iteration [19]. Potential publication bias was examined using funnel plots [20]. The calculations were performed using the Meta—Disc 1.4 statistical software.

Results

169 studies were identified from the initial search, we excluded 146 studies for the following reasons: reviews or case reports, the publications dealt with other topics, duplication of data, or not available as full text articles. Finally, we identified 23 studies represented data from 1478 PD patients for the meta-analysis [1,11,12,21-39]. In 14 articles, PD patients were diagnosed according to the United Kingdom Parkinson's Disease Society Brain Bank Criteria (UK). In 9 articles, PD patients were diagnosed according to the Movement Disorder and Parkinson's Disease Group of the Chinese Medical Association Branch of Neurology (Chinese diagnosis criteria) [14]. The main characteristics of all included studies were summarized in Table 1. There was significant statistical heterogeneity among the studies, thus, a random effect model was employed. The pooled sensitivity of TCS for the diagnosis PD was 78% (95% CI: 0.75, 0.80) (Figure 1) and the pooled specificity was 87% (95% CI: 0.85, 0.89) (Figure 2). The pooled LR+, LR- and DOR of TCS were 6.74 (95% CI: 5.04, 8.31) (Figure 3), 0.23 (95% CI: 0.19, 0.28) (Figure 4) and 31.32 (95% CI: 21.28, 46.09) (Figure 5), respectively. The ROC plane did not revealed no heterogeneity secondary to the threshold effect (Figure 6). In addition, the AUC and Q index showed in the symmetric SROC curve was 0.9119 and 0.8442, respectively, which reflected the overall high level of accuracy (Figure 7). The results were consistent when we performed a secondary analysis by repeating the meta-analysis and omitting each study at each iteration. Publication bias may be acceptably low because all the funnel plots on the diagnostic value of TCS in the Chinese PD patients for the included studies did not reveal obvious signs of publication bias (Figure 8).

Furthermore, we used five items to separate subgroup analysis: the publication year (2010–2015; 2016–2018), age (≤65, >65), sample size (≤50; >50), diagnosis criteria of PD (UK; Chinese diagnosis criteria), and male ratio (≤55%, >55%). The studies taking place in 4 years ago had higher sensitivity, specificity, LR+ and DOR than those in the last 4 years (0.8vs.0.74, 0.87 vs.0.86, 6.51vs.6.18, 33.18vs.25.98, respectively), but lower LR- (0.22vs.0.26). The sensitivity, specificity,

Table 1. Characteristics of studies included in the meta-analysis

Author	Years	Diagnosis criteria	Number of PD	Male rido (%)	Ages	TP	FP	FN	TN
Feng AZ	2012	Chinese diagnosis criteria	30	53.33	54.3±7.9	25	3	5	27
Qiao YN	2016	Chinese diagnosis criteria	89	52.8	61.1	81	5	8	79
Liu X	2018	Chinese diagnosis criteria	38	47.37	69.37±9.86	28	3	10	39
Xu HW	2017	Chinese diagnosis criteria	51	52.9	69.51±3.49	41	12	10	39
Liu X	2013	Chinese diagnosis criteria	42	81.9	62±14	39	3	3	47
Zhuang JJ	2015	Chinese diagnosis criteria	36	58.33	62.63±7.57	32	2	4	30
Hu HY	2016	Chinese diagnosis criteria	100	57.27	61.7±5.7	73	5	27	45
Wang XP	2017	Chinese diagnosis criteria	51	55.97	68.31	41	13	10	37
Yang LJ	2012	Chinese diagnosis criteria	53	56.6	69.3±7.3	40	7	13	46
Zhu JW	2018	UK	36	52.78	61.7±11.2	29	5	7	36
Luo WF	2012	UK	110	49.1	58.7	88	11	22	99
Sheng YJ	2012	UK	78	48.71	62.2	66	5	12	55
Zhang YC	2010	UK	80	56.5	60.7±11	58	10	22	70
Zhang LL	2018	UK	65	53.8	65.34±10.68	42	6	23	47
Chen J	2013	UK	30	60	47.3±5.18	25	2	5	28
Liu XJ	2018	UK	30	60	56.5±5.01	25	1	5	27
Wang R	2011	UK	34	61.76	64.11±10.25	31	4	3	34
Cao CJ	2017	UK	122	64.75	60.0±10.5	91	3	31	37
Li C	2013	UK	92	56.5	62.23	74	26	18	73
Zhou HY	2016	UK	201	69.15	61.43	124	17	77	75
Dong ZF	2017	UK	38	57.89	67.3±8.6	31	3	7	23
Yang J	2017	UK	30	57.14	65.4	24	2	6	28
Zhang ZH	2015	UK	42	66%	65.2±7.3	38	9	4	39

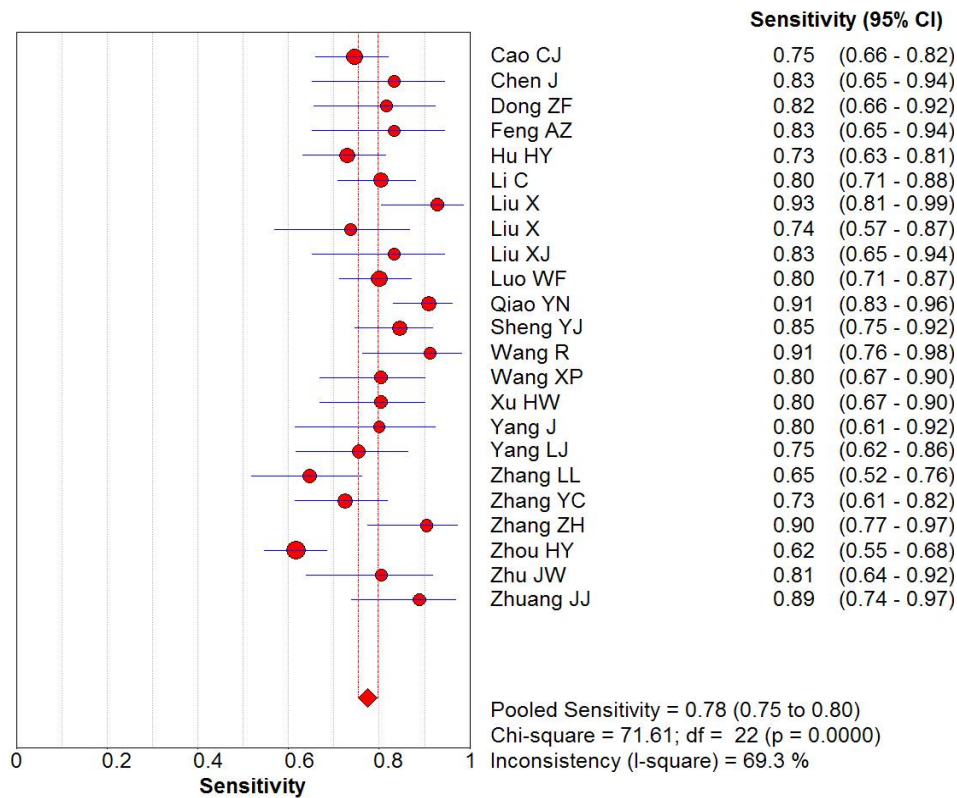


Figure 1. The sensitivity of transcranial sonography for the diagnosis of Parkinson's disease in the Chinese population

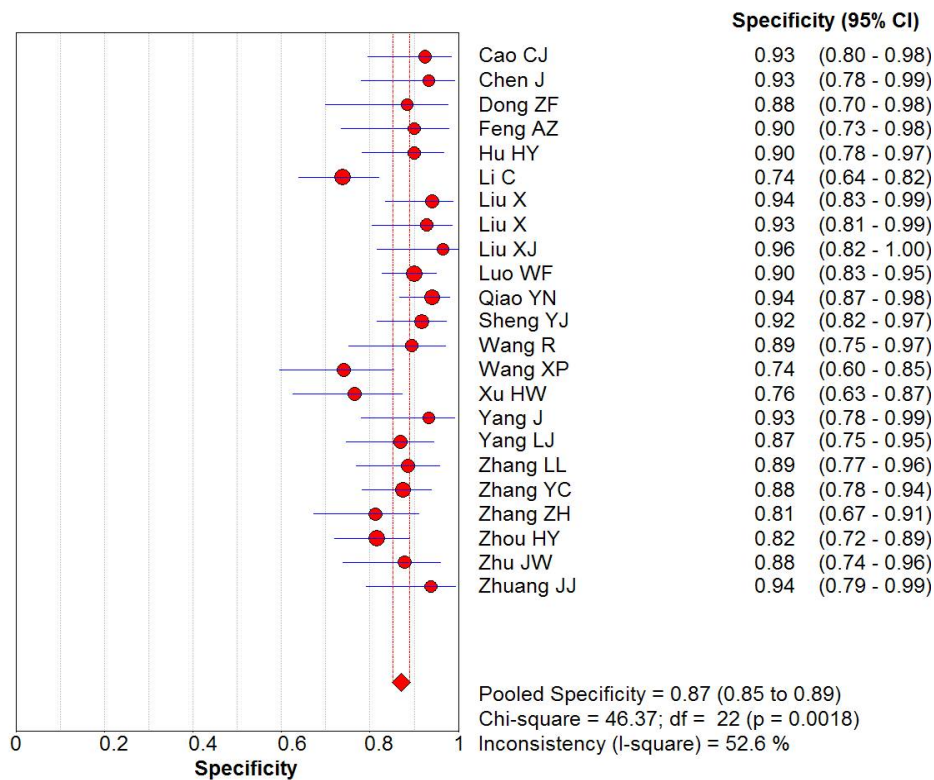


Figure 2. The specificity of transcranial sonography for the diagnosis of Parkinson's disease in the Chinese population

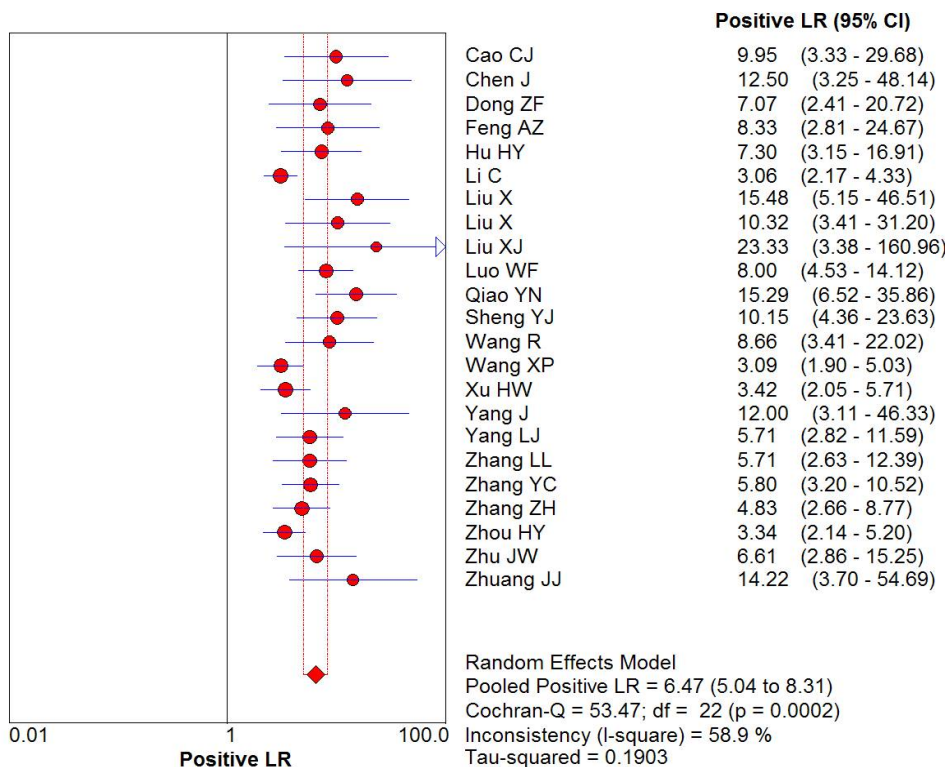


Figure 3. The positive likelihood ratio of transcranial sonography for the diagnosis of Parkinson's disease in the Chinese population

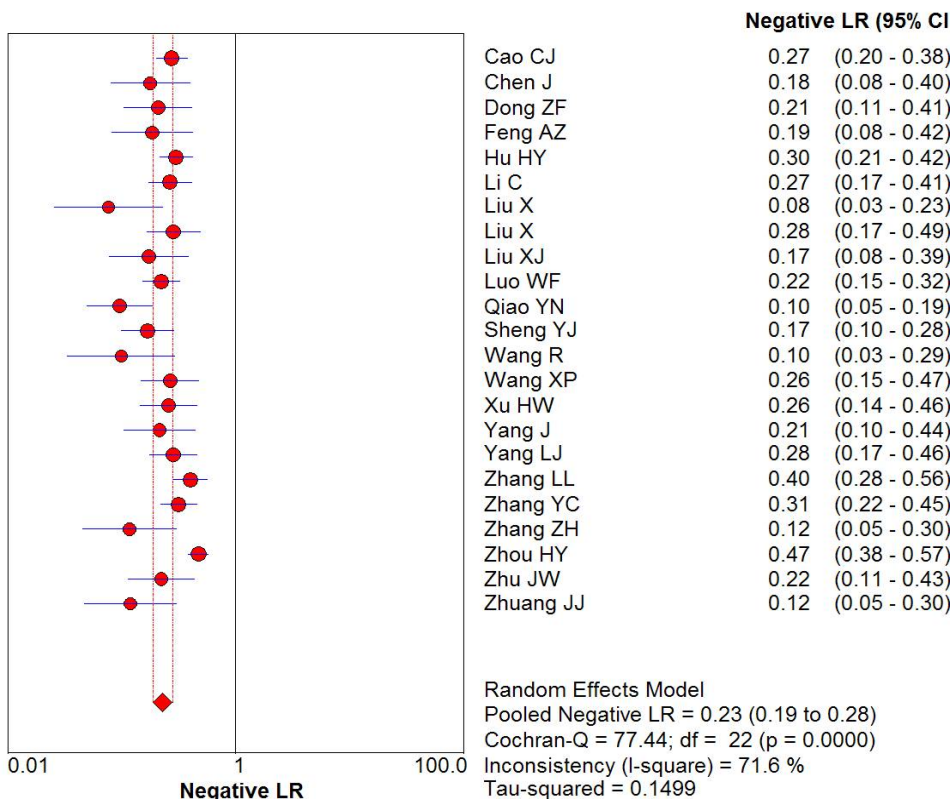


Figure 4. The negative likelihood ratio of transcranial sonography for the diagnosis of Parkinson's disease in the Chinese population

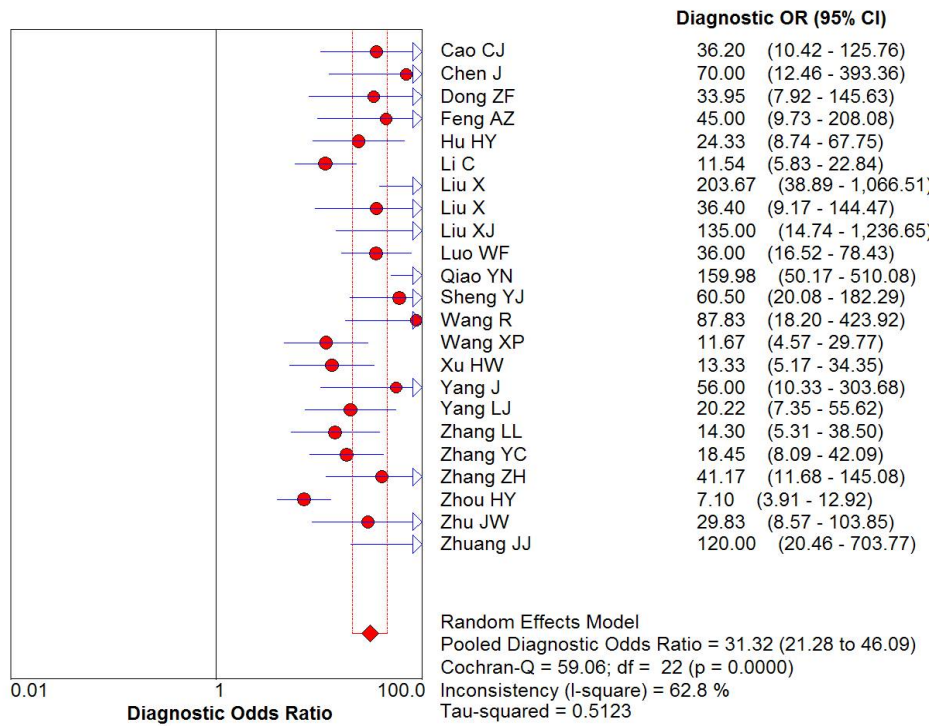


Figure 5. The diagnostic odds ratio of transcranial sonography for the diagnosis of Parkinson's disease in the Chinese population

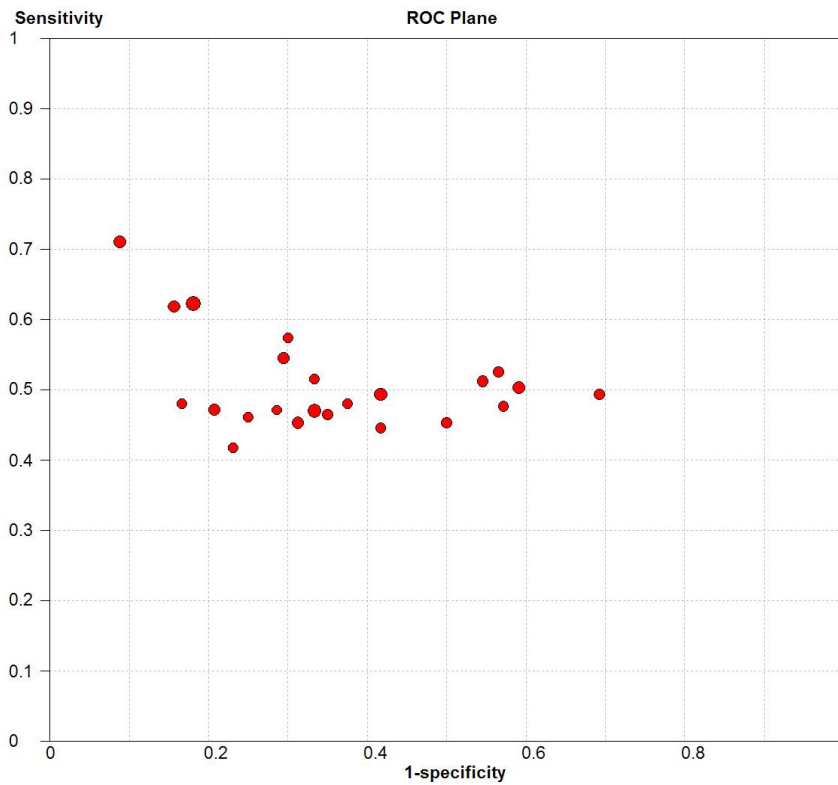


Figure 6. Sensitivity versus 1-specificity in ROC plane for each included study

LR+, LR- and DOR for the studies with age>65 were 0.77, 0.84, 4.81, 0.27, 19.9 respectively; while for those with age≤65, the results increased to 0.78 (sensitivity), 0.88 (specificity), 7.63 (LR+), 39.72 (DOR), but LR- reduced to 0.21. The sensitivity, specificity, LR+ and

DOR of TCS for the studies with a sample size below 50 individuals was higher than those with a sample size over 50 (0.85vs.0.75, 0.91vs.0.85, 8.11vs.5.38, 55.95 vs.21.33, respectively), besides LR- (0.18vs.0.27). The sensitivity, specificity, LR+ and DOR of TCS for the subgroup with Chinese diagnosis criteria was higher than those with UK (0.82vs.0.76, 0.88vs.0.87, 7.11vs.6.17, 37.55vs.27.94, respectively), except the LR- (0.21vs.0.24). The last one, the sensitivity, specificity, LR+, LR- and DOR of TCS for the studies with more male PD patients was lower, (0.76vs. 0.79, 0.85vs.0.89, 6.13vs.6.96, 0.85vs.0.89, 31.73 vs. 31.90, respectively). The results of the subgroup analysis were shown in Table 2. To determine the effect of these factors for the heterogeneity, we further conducted a meta-regression analysis with the covariates which included in subgroup analysis. Notwithstanding, when the meta-regression analysis was performed, the sample size was the important cause for the heterogeneity (P=0.0051), Table 3.

Discussion

Numerous ultrasound studies have suggested that a typical enlarged area of echogenicity in the substantia nigra can help diagnose PD in European and American [40,41]. However, it is still unknown the exact diagnostic accuracy of substantia nigra hyper-echogenicity by TCS for the diagnosis of PD in the Chinese population. Some studies [23,26] found that PD patients had high incidences of SN hyperechogenicity detected by TCS, and TCS could improve the specificity of diagnosis for PD. However, Zhang YC, *et al.* [22] reported that TCS might provide some valuable information for clinical diagnosis of PD, but some of the older individuals were unsuitable to the exam for their unadequated temporale bone windows. Until now, there is no consensus on whether TCS is a useful and accurate method in the Chinese population. So, further studies are required to identify the diagnostic value of TCS in detection of PD in the Chinese population. To our knowledge, the present study is the first meta-analysis determining diagnostic value of TCS in the diagnosis of PD in the Chinese population. Our study showed the pooled sensitivity and specificity of TCS were 78% and 87%, respectively. The results of the current study are consistent with previous findings in European populations [42,43]. As we expected, in the subgroup of sample size, studies that used larger sample size (>50) would report a lower sensitivity, specificity, LR+, and DOR, while a higher LR-. Moreover, the sample size was confirmed to be the significant cause of heterogeneity in the meta-regression analysis (P=0.0051). In our study, the age and male ratio subgroups showed the lower sensitivity, specificity, LR+, and DOR, while a higher LR-.

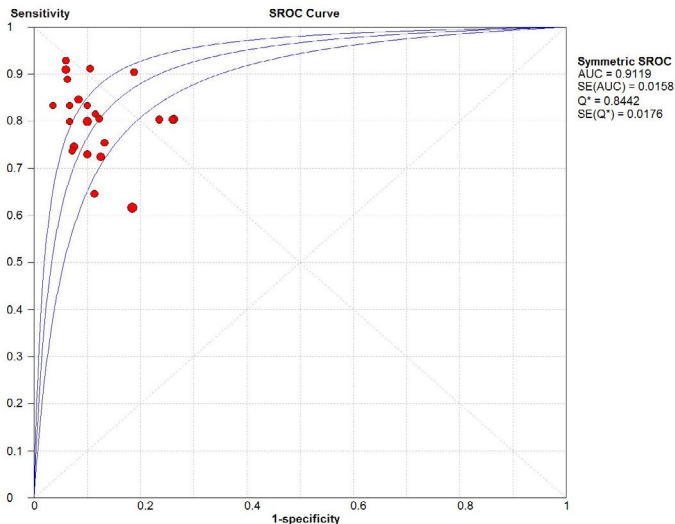


Figure 7. SROC of the accuracy of transcranial sonography for the diagnosis of Parkinson's disease in the Chinese population

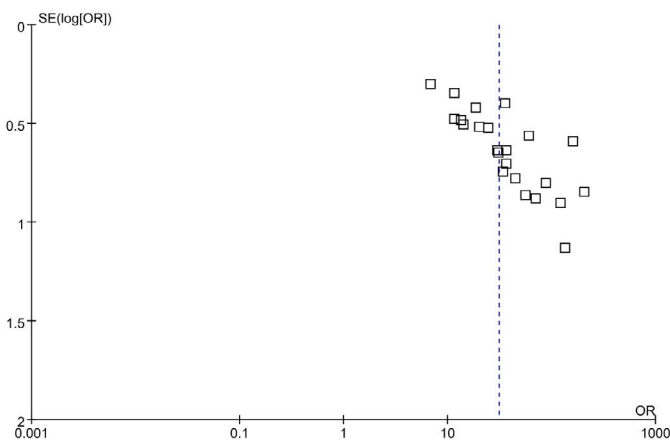


Figure 8. Funnel plots for the included studies

Table 2. Subgroup analysis of the diagnostic value of transcranial sonography in Parkinson's disease

Subgroup	Number of studies	sensitivity (95% CI)	specificity (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)	diagnostic OR (95% CI)
Publication year						
2010–2015	11	0.80 (0.77;0.83)	0.87 (0.84;0.89)	6.51 (4.54;9.34)	0.22 (0.15;0.31)	33.18 (18.18;60.58)
2016–2018	12	0.74 (0.71;0.77)	0.87 (0.84;0.90)	6.18 (4.28;8.92)	0.26 (0.20;0.34)	25.98 (14.75;45.76)
Sample size						
≤50	11	0.85 (0.81;0.88)	0.91 (0.87;0.93)	8.11 (5.97;11.02)	0.18 (0.15;0.23)	55.95 (35.23;88.85)
>50	12	0.75 (0.72;0.78)	0.85 (0.83;0.88)	5.38 (3.95;7.33)	0.27 (0.22;0.34)	21,33 (13.37;34.37)
Diagnosis criteria of PD						
UK	14	0.76 (0.73;0.78)	0.87 (0.84;0.89)	6.17 (4.58;8.31)	0.24 (0.19;0.31)	27.94 (17.49;44.64)
Chinese diagnosis criteria	9	0.82 (0.78;0.85)	0.88 (0.85;0.91)	7.11 (4.41;11.47)	0.21 (0.15;0.29)	37.55 (18.89;74.66)
Age						
≤65	15	0.78 (0.75;0.80)	0.88 (0.86;0.90)	7.63 (5.37;10.84)	0.21 (0.16;0.28)	39.72 (22.82;69.13)
>65	8	0.77 (0.73;0.82)	0.84 (0.80;0.88)	4.81 (3.55;6.57)	0.27 (0.22;0.34)	19.94 (13.36;29.72)
Male ratio						
≤55	9	0.79 (0.76;0.83)	0.89 (0.86;0.92)	6.96 (5.03;9.63)	0.23 (0.18;0.31)	31.90 (19.20;53.01)
>55	14	0.76 (0.73;0.79)	0.85 (0.83;0.88)	6.13 (4.36;8.62)	0.22 (0.17;0.37)	31.73 (18.27;55.18)

Table 3. Meta-regression analysis of potential moderators to explain heterogeneity of diagnostic value of transcranial sonography in PD

	Meta-regression coefficient	SE	P	RDOR	95% CI
Publication year	-0.329	0.3673	0.3838	0.72	0.33;1.57
Sample size	-1.121	0.3459	0.0051	0.33	0.16;0.68
Diagnosis criteria of PD	-0.554	0.3481	0.1313	0.57	0.27;1.20
Age	-0.561	0.3760	0.1548	0.57	0.26;1.27
Male ratio	-0.258	0.3306	0.4473	0.77	0.38;1.56

The results indicated gender and age were the factors relating higher incidences of SN hyperechogenicity, which were consistent with previous study [26]. However, Zhuang JJ, et al. reported that the area of bilateral substantia nigra echo was negatively correlated with gender, but positively correlated with age [30]. Additionally, Zhou HY, et al. thought that males had larger SNL echogenic areas compared to females, while age had no effect on the SN echogenic areas [1]. Thus, further studies are required to address this issue. In the subgroup of diagnosis criteria of PD, the result is also significantly different. The sensitivity, specificity, LR+ and DOR of TCS for the subgroup with Chinese diagnosis criteria were higher than those with UK, except LR-. But in the further meta-regression analysis, the diagnosis criteria were not the cause of heterogeneity (P=0.1313). Therefore, we could use both UK and Chinese diagnosis criteria to diagnose PD patients in our daily work.

Although SN hyperechogenicity is a common feature of PD patients, the quality of the temporal bone window might cause the difference for the diagnosis by using TCS. And 10–20% European were excluded from TCS studies due to this issue [44]. In China, TCS examination failed in 8.08–12.08% of the individuals [22], which was much lower than previous reports. We speculated that the differences might be explained by the racial differences in the temporal skull thickness and the size of brain between European and Asian [45]. In addition, some included studies found that SN echogenicity significantly correlated with UPDRS part II scores in the Chinese PD patients [26,30], suggesting that increased SN echogenicity might reflect more severe disease disability or poorer response to medication. However, due to the relatively low penetration rate and relatively low sensitivity of TCS, there is a need to demonstrate these findings in the future studies.

Overall the evidence for the use of TCS was strong; our study also had several limitations. First, although our study had a large sample size compared to most of the previous studies, the sample size in some of the included studies was small. We have found that sample size was the important cause for the actual prevalence of heterogeneity in our meta-regression analysis. Second, the heterogeneity among the studies was significant. Although we attempted to find the causes of it by conducting subgroup analysis and meta-regression analysis, the heterogeneity among studies persisted. Finally, almost all these studies were retrospective and involved patients with well-established diagnoses and long-disease duration. Therefore, prospective cohort study for diagnostic accuracy would be practically difficult but important for future research.

Conclusion

In summary, our present study demonstrated that SN hyperechogenicity could help to discriminate PD from healthy controls; TCS was a useful and accurate method in the diagnosis of PD in the Chinese population. However, TCS had its own limitations, which included its dependency on the bone window and operator experience.

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Conflicts of interest

We have no conflicts of interest regarding the content of this article.

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